THE
ULSTER MEDICAL JOURNAL

PUBLISHED ON BEHALF OF THE ULSTER MEDICAL SOCIETY

Vol. X 1st NOVEMBER, 1941 No. 2

Generalised Neurofibromatosis

By J. H. BIGGART, M.D., D.SC.

Professor of Pathology, Queen's University, Belfast

WHILST neurofibromatosis, in more or less localised form, is not infrequently seen, most of our knowledge concerning the histological structure of the nodules is gained from biopsy specimens. The following case, illustrating as it does the widespread distribution of the process and the nature of the associated lesions, seemed, therefore, worthy of report.

CLINICAL HISTORY.

The patient, a man of fifty years of age, was admitted to the Royal Infirmary, Edinburgh, complaining of pain in his left foot and some weakness in the right arm. A week prior to admission he had noticed that the middle toe of the left foot was swollen and painful. The swelling evidently arose in relationship to a corn. The pain and swelling increased, and the skin finally broke down with the discharge of pus.

The weakness in the right arm had developed during the past eight months. It was accompanied by a feeling of numbness and tingling. These symptoms had become much more marked in the two months prior to admission.

On examination, the middle toe of the left foot was found to be the site of a marked infective necrosis with a thick purulent discharge. The adjacent toes were also red and swollen.

There was a well-marked generalised von Recklinghausen's disease, the whole body being covered by multiple pedunculated and pigmented nodules. There was weakness of the muscles of the right upper limb, most marked in the flexor group of muscles, but present also in the extensors. Wasting and weakness of the small muscles of the thumb and the first dorsal interroseous muscle were present. There was little appreciable loss of sensation in the affected arm. A hard immovable swelling was found in the right side of the neck. This was pyramidal in shape, the apex reaching as high as the cricoid cartilage, whilst the base continued into the thorax underneath the clavicle.

Other examinations were essentially negative. The blood-pressure was 150/90. The infected toe was amputated, but the patient died fourteen days later from a rapid terminal enlargement of the tumour in the neck. The clinical impression was, that one of the nodules of the von Recklinghausen's disease had become sarcomatous.

AUTOPSY (437/36).

The body is that of a well-developed male of middle age. Scattered diffusely over the trunk are numerous small tumours, averaging one to two mm. in diameter. Some of these are pedunculated; some sessile. All of them are of subcutaneous origin. A few similar nodules are also found on the proximal parts of the limbs, but their distribution is irregular and cannot be said to follow the course of any particular nerve or nerves. Associated with these tumours there is a marked degree of pigmentation. This is not diffuse, but appears in small patches resembling freckles. These are not present over the face or hands. In the right supra-clavicular triangle there is a large firm mass, which displaces the trachea towards the left.

Body cavities.—The pericardial sac is normal. The apex of the right lung is slightly adherent to, but easily separated from, the tumour, which extends down into the mediastinum as far as the level of the bifurcation of the trachea. There is a fibrino-purulent exudate over the base of the right lung. The peritoneal cavity contains no free fluid.

Heart.—This is of normal size. The epicardium is thin and translucent. There are no lesions in the right auricle or ventricle. The left ventricular wall shows no hypertrophy. The endocardium is thin and the valves normal. Atheromatous changes are marked in the coronary arteries.

Lungs.—There is a fibrino-purulent exudate over the diaphragmatic surface of the left lung. This lung is heavier than normal, and on section numerous small peribronchiolar areas of consolidation, which are becoming confluent, are found. The dark colour of these areas suggests that there may have been some aspiration of gastric contents. The lining of the bronchi is œdematous and congested. The bronchial glands are not appreciably enlarged.

The right lung shows a smooth pleura, which is lightly adherent to the tumour mass in the region of the apex. The upper and middle lobes are crepitant. The lower lobe shows a patchy consolidation similar in type to that seen in the left lung. The peribronchial lymph-nodes show congestion, but no metastases.

Spleen.—This is of normal size. The capsule is thin. On section, the malpighian corpuscles are distinct. The pulp is red, but not softened. The vessels are thickened, and the trabeculæ prominent.

Liver.—This is of normal size and shape. There are no glands in the hilum, though the gastro-hepatic ligament is greatly thickened. The common bile-duct is patent and the gall-bladder normal. On section, the liver lobules are quite distinct, though their central zones are pale. The bile-ducts and radicles of the portal vein are patent.

Pancreas.—The ducts are patent. On section, the acinar tissue appears normal.

There are two small nodules about three mm. in diameter attached to branches of the sympathetic nerves on the posterior surface of the head of the gland.

Stomach and Intestine.—The stomach shows nothing of note. At the duodeno-jejunal junction there is a small (four mm.) nodule on the serous surface. The terminal ileum shows several adhesions and much thickening of the mesentery. There is some black pigmentation of this area. A large inguinal hernial pouch is found with similar pigmentation, and the findings suggest that there has been a herniation of the terminal ileum with subsequent reduction and fibrotic repair of the damaged mesentery.

Genito-urinary system.—The kidneys are of normal size. The capsule strips easily, leaving a smooth homogeneous surface. On section, the organs appear acutely congested, but the cortex is of normal width and the striæ regular. The medulla shows nothing of note. The pelvis is normal. There is some atheroma of the renal arteries. The ureters and bladder show no lesions.

Adrenals.—These appear to be of normal size. Both together weigh 17 gm. On section, the cortex is of normal width, and appears well filled with lipoid. The medulla of the right gland is of normal size. That of the left gland shows a small circumscribed nodule, 3 mm. in diameter. On this side also there is an elongated tumour, 2.5 cm. by 0.7 cm. by 0.5 cm., on a branch of the sympathetic plexus running to the gland.

Neck organs.—There is a large piece of orange impacted in the œsophagus at the level of the bifurcation of the trachea. At this level there is some narrowing of the lumen from pressure by the adjacent neoplasm.

The trachea is congested, but does not appear compressed, though it is displaced well towards the left.

The thyroid is rather small. On section, it appears to be a normal colloid-containing gland. The parathyroids are not enlarged.

The mass in the right supra-clavicular region extends downwards into the upper part of the right thorax and medially into the mediastinum (fig. 1). It can be easily separated from the surrounding structures. The trunks of the right brachial plexus appear to emerge from its lateral surface, whilst the three lower cervical roots enter into its medial surface. The phrenic nerve appears to course through the centre of the tumour, and, whilst thickened, can be quite easily dissected from the tumour (fig. 1). On section, the tumour appears as a white, hard, structureless mass with a few scattered areas of necrosis. The external jugular vein which courses over its anterior surface shows a recent thrombosis. The carotid artery runs for some distance through the tumour, but is apparently normal.

The aorta shows only a little atheroma.

Brain.—The dura is normal. The meninges over the left temporal lobe are thickened and rather opaque. The brain appears large. The vessels at the base are dilated, but not atheromatous. There are no tumours on the acoustic or optic nerves. Section following fixation shows nothing of note.

Hypophysis.—This is of normal size, but slightly compressed by arterio-sclerotic internal carotid arteries. On section, nothing abnormal is noted.

Spinal cord.—Naked-eye examination of the spinal cord shows no lesions. A small circumscribed nodule is present on one of the roots of the cauda equina. Apart from this, the dorsal nerve-roots appear quite normal in their course inside the dura. Several of the dorsal-root ganglia, however, in the lumbar region are enlarged to three or four times their normal size, and from these greatly thickened nerves arise.

Peripheral nervous system.—The right brachial plexus as it emerges from the tumour already described, is found to consist of trunks, which are four to five times their normal diameter (fig. 1). They feel extremely hard. This increase in size is continued into all the branches of the plexus. On the nerve to the teres major (fig. 1) is a large fusiform swelling, 6 x 3 x 3 cm., which on section is seen to be composed of a rather hard but translucent tissue. The left brachial plexus is not so markedly enlarged, but there are definite fusiform enlargements on the median trunk.

The lingual and hypoglossal nerves show a diffuse thickening.

The sacral plexus is very definitely enlarged, the various roots feeling varicose, and on section showing a rather uneven but diffuse thickening. The right sciatic nerve is immense. As it is followed down the leg, it shows a large fusiform swelling. Here the nerve is 3 cm. thick and 5 cm. broad. This increase in diameter is continued into its branches. Longtitudinal and transverse sections of these parts of the nerve which appear merely diffusely thickened, show many small hard translucent nodules occurring in the course of its component nerve bundles.

The left sciatic nerve appears only slightly enlarged. A few firm nodules can be felt in its substance, and these become more obvious in the posterior tibial nerve. On a branch of the external popliteal nerve, about three inches above the external malleolus, is a large fusiform swelling, 8 x 4 x 3 cm. (fig. 3). In structure it resembles that found on the nerve to the teres major.

Practically all the peripheral nerves show irregularity in their contour. Sometimes it is a diffuse increase in size. In others it is definitely nodular, and the nodule may affect the whole or part of the diameter of the nerve, or of individual nerve bundles. Occasionally the mass is large, as in the case of the large fusiform tumours described above.

Autonomic nervous system.—This is affected in like manner and to the same degree as the peripheral nervous system.

The right recurrent laryngeal nerve and some of the branches of the vagus are three times their normal diameter. The left thoracic chain appears relatively normal. The right shows a large fusiform swelling at the level of the sixth thoracic segment (fig. 3), and there is enlargement of the seventh thoracic ganglion. The cœliac ganglion is slightly enlarged, and its branches to the viscera are everywhere prominent, some of them measuring 3 mm. in diameter. The thickening and varicosity of the plexus in the gastro-hepatic omentum has led to an apparent thickening of this structure. The nerves to the adrenals are prominent, and one branch to the left adrenal shows the fusiform swelling (2.5 x 0.5 x 0.5 cm.) already noted. The hypogastric and internal iliac plexuses show no apparent deformity,

but all their branches are more readily identified and may be a little thicker than normal.

Microscopical Examination.

In all, over sixty blocks of the various tissues have been examined by various methods, but detailed descriptions will only be given of those sections which show changes pertinent to the disease process in the nervous tissues. The patient died from a broncho-pneumonia, which was evidently the result of the aspiration of gastric contents. The parenchymatous tissues of the heart, liver, pancreas, and kidneys show little of note. Thyroid, testes, parathyroids, and hypophysis are normal.

Adrenals.—The right adrenal shows no lesions. Some of the small perivascular branches of the autonomic nervous system show an intense cellularity, which appears to be due to a proliferation of the neurilemmal cells. The left adrenal appears slightly enlarged. The section shows two small nodules of entirely different structure, which extend from the region of the central vein through the medulla and cortex to the periadrenal fat. One of these, the more central, is composed of large polygonal cells resembling those of the normal adrenal medulla, but three to four times as large. These large cells have a loose alveolar arrangement, the only stroma being a meshwork of capillaries. Some of these cells contain a melanin pigment; others show various forms of intracytoplasmic inclusion bodies, which in most instances are strongly acidophilic. All of these cells give a positive chromaffin reaction. The nuclei are large and vesicular, and in some instances show much resemblance to the nuclei of ganglion cells. The tumour projects into the adrenal vein, and fills about two-thirds of its lumen. This intravascular projection is still covered by the vascular endothelium, and there is no thrombosis. The tumour appears to have the characteristics of a chromaffinoma (phæochromocytoma).

The other nodule (3 mm. in diameter) is composed of whorls of axis cylinders, separated by fine bands of fibrous tissue fibrils running parallel to the axis cylinders. In the nodule one finds a few scattered ganglion cells, some of which are binucleated.

Peripheral nerves.—The large tumour in the right supra-clavicular region is composed of interlacing bands of large spindle-shaped cells with oval nuclei (fig. 6). These nuclei have a vesicular pattern of chromatin, and mitotic figures are common. The tumour is found to be infiltrating many of the smaller blood-vessels. It is worthy of note, however, that no metastases were found in the lungs, brain, liver, vertebral column, or skull. Silver stains show a large amount of reticulum. The cells themselves have long bipolar cytoplasmic processes. Areas of necrosis, secondary to the vascular occlusion, are common.

The tumour involves the trunks of the brachial plexus. These trunks are infiltrated by the tumour-cells. There is no spread along the perineural lymphatics. Instead, the tumour seems to spread directly along the nerve-tissue itself, and adjacent small nerve-twigs are almost completely replaced by this intraneural sarcomatous growth.

Histological examination of other nerves reveals a process which can best be

described in general form. Nerves showing no actual growth are seen to be generally thickened. This thickening is due to a laying down of fine fibrils of fibrous tissue parallel to the course of the myelin sheaths—a fibrosis very comparable to the gliosis which occurs in the tracts of the spinal cord in a plaque of disseminated sclerosis, and which might well be described as an "isomorphic fibrosis." This fibrous tissue bears a very intimate relationship to the essential nervous tissue, forming, as it were, a sheath around each individual myelin sheath. In such diffusely thickened nerves the perineurium appears quite normal, and it is obvious that the new formation of fibrous tissue does not arise from the perineurium, but from one of the more intimate sheaths of the nerve-fibre. In other areas the process may be apparent as a nodule on the course of the nerve. In the less complicated of such nodules one merely finds a local exaggeration of the more diffuse change described above. There is more fibrous tissue around the nerve fibres, and in Weigert-Pal preparations the myelin sheaths are found widely separated by this new fibrous formation, but they still course unimpaired through the nodule, and show their normal appearance when they finally emerge distal to it. In the larger nodules, however, such as those found on the right sciatic, left external peroneal, etc., whilst some of the myelin sheaths can still be stained, others have disappeared. Axis cylinder stains show that the myelin-sheath stains give an erroneous impression of the number of nerve-fibres coursing through the tumour. It would appear that some naked axis cylinders persist, even after destruction of the myelin sheaths. These larger nodules show a hyaline change in the fibrous tissue around the vessels, and a curious granular groundwork, which does not give a positive reaction with mucicarmine, between the bundles of reticulum.

This description fits most of the histological changes seen in the nodules. However, it is apparent from the description that we are dealing with the end-result of a proliferative lesion, and accordingly careful search was made for foci of active progression. Such were found in a nerve in the vicinity of the left adrenal, and in a branch of the left brachial plexus. Individual nerve-fibres in the more chronic lesions also showed phases of activity. In these areas the cellular reaction appears to be limited to individual nerve fibres. Surrounding one myelin sheath, or occupying the space where a myelin sheath had been, one finds a proliferation of three or four neurilemmal cells apparently forming a syncytium (fig. 8). Around these is a fibrous-tissue sheath. This sheath seems to become thicker and fibrous septa appear between the proliferating intra-sheath cells. Even in the active areas it is difficult to find any evidence of cellular activity in the interstitium of the nerve. In these active areas the perineurium seems to play no part in the proliferative process.

In the larger and older nodules a curious syncytium is found surrounding the bundles of reticulum. This cellular syncytium, however, is not an intrinsic part of the process. It is not constant. It is not seen during the active proliferative phase.

The skin, or rather subcutaneous nodules, show a histological appearance which is more difficult of analysis. Nerve-fibres can be traced into these growths. For

the most part, however, they consist of interlacing bands of cells, the origin of which cannot be so clearly seen as in the nodules occurring in the larger nerve-trunks. In some instances microscopical lesions surround the sweat glands, and suggest an origin from the autonomic nerve supply of these structures (fig. 5).

Dorsal-root ganglia.—The process resembles in all details that already described. There is a multiplication of the capsular cells, and in a few instances these have completely replaced the ganglion cells.

Autonomic nervous system.—The nodules and diffuse thickenings found in the autonomic nervous system duplicate in structure those found on the somatic nerves. Histological examination shows that the neurofibromatous change is extremely widespread. Apart from the gross changes noted at autopsy, small perivascular nerves in the liver, pancreas, renal pelvis, and lungs show similar neurilemmal proliferations and intraneural fibrosis.

Brain.—There is some ependymitis, and some periaqueductal gliosis, but neither of these changes appears of neoplastic character. No changes comparable to those seen in tuberous sclerosis, and no glial nodes are found. The cranial nerve-roots show no lesions.

Spinal cord.—The nodule already noted on the cauda equina shows much the same histological structure as that found in the nodules on the peripheral nerves. Axis cylinders are present, and there are none of the histological characters of the more usual neurinoma. Nothing abnormal is seen in the cord-substance.

Anatomical diagnosis.—

Septic gangrene of toe.
Generalised neurofibromatosis of peripheral and autonomic nervous systems.
Chromaffinoma of left adrenal : ganglioneuroma of left adrenal.
Sarcomatous change in neurofibromatous nodule in right supra-clavicular region.
Pressure upon trachea and œsophagus.
Aspiration pneumonia.

Discussion.

The present case furnishes an additional record of the association of generalised neurofibromatosis with other anomalies of the nervous system. The histological studies seem to help in the elucidation of the pathogenesis of the neoplastic process. Verocay (1910) first pointed out that tumours of the peripheral nerves were not due to a simple connective tissue hyperplasia. The palisading of the nuclei, however, which he emphasizes is a well-recognised histological feature of the solitary neurinoma, but is by no means characteristic of von Recklinghausen's disease, though small areas of this type of tissue in the nodules may undoubtedly occur. Masson (1932) has produced experimentally proliferations of the neurilemmal cells, which show many of the characteristics of the neurinoma, and which seem to have convinced this investigator that the neurilemmal cell is the cell-type of these tumours, and also that this cell may produce a type of argyrophilic reticulum. However, the application of Verocay's views to neurofibromatosis has not met with

general acceptance (Kaufman, Stout), and so in the analysis of the present case attention has been concentrated on those histological features which might support or refute the essential neural origin of the tumours. As will be noted from the microscopical description of the lesions, active cellular proliferation occurs in the early stages inside the membrane surrounding each myelin sheath. At this stage no other cellular activity is encountered. The perineurium remains normal; there is no cellular activity in the fibrous septa of the nerve-bundles, and no cellular activity, which might be interpreted as endoneurial, outside the neurilemmal sheath. The proliferating neurilemmal cells preserve their syncytial character. In this stage the myelin sheath may disappear, but there is usually preservation of the axis cylinder. Connective tissue fibrils then appear between the proliferated nuclei, and these seem always to be laid down parallel to the long axis of the neurilemmal cells, and therefore parallel to the original nerve-fibre. In some instances the syncytial cytoplasm of the proliferating neurilemmal cells is seen divided, as it were, into compartments by these fibrils. This process seems to proceed until the nerve-fibre, with or without its myelin sheath, is completely surrounded by a fine bundle of parallel reticulum fibres, which appear to be still enclosed in the original but somewhat thickened neurilemmal sheath. In this process there seems occasionally to be some lengthening and tortuosity of the original nerve-fibre, for even on transverse section a few myelin sheaths may be found running transversely for various distances. An accentuation of this lengthening and tortuosity results in the appearance of the plexiform type of tumour.

In all this period of activity our histological observations tend to agree with those of Masson, that it is the neurilemmal cells, and these alone, which proliferate. However, the nature of the material renders it difficult to be certain that the reticulum is formed by these cells, and that it may not be laid down by the endoneurium in response to the activity of the neurilemmal cells. Doubts as to the exact nature of the endoneurium have recently been raised by Masson (1932). This author states that the structure which has been called endoneurium, may be divided by histological analysis into two systems. Firstly, there is an interstitial connective tissue-fibre lying in the angle where three nerve-fibres meet. This system cannot be held responsible for the sheath-like proliferation of connective tissue-fibrils. Secondly, there is a fine fibrillar sheath around each individual nerve-fibre—the Plenk-Laidlaw sheath. This sheath, which consists of delicate interlacing fibrils, is closely applied to the neurilemmal cells, and Masson's studies seem to indicate that it is part of the neurilemmal sheath rather than a distinct entity. In neurofibromatosis, therefore, whilst the cellular activity appears confined to the neurilemmal cells, the actual multiplication of fibrils occurs in connection with this Plenk-Laidlaw sheath.

In the older nodules the proliferated cells disappear, and one finds relatively acellular bundles of reticulum, in which, however, it is sometimes possible to demonstrate the original axis cylinder. In these too one finds a curious finely granular ground-substance between the bundles of fibrils. The nature of this substance and its derivation cannot be settled from histological examination

alone. It does not give a positive reaction with mucicarmine. Running through this groundwork, and surrounding the individual fasciculi, is a cellular syncytium. The cells composing this syncytium appear to be of endoneurial origin. The cells of the normal endoneurium show the same anastomotic prolongations and the same thin membrane of cytoplasm around their nuclei. These anastomosing cells, however, cannot be regarded as an essential part of the process. They tend to be most prominent in those areas where the cellular activity of the neurilemmal sheath has ceased : they may only be formed in one part of the nodule; and they are not obvious in the early proliferative stages of the process.

It would appear, therefore, that in neurofibromatosis the active process is on the part of the neurilemmal cells, analogous to the process which Verocay suggested, and Masson seems to have demonstrated in respect of the neurinoma. The different histological appearances of the two types of growth—the neurofibroma and the neurinoma—seems to be due to the fact that, whereas in the neurinoma there are no myelin sheaths or axis cylinders and the cellular proliferation is independent of these structures, in the neurofibroma the cellular activity occurs in relationship to individual nerve-fibres, which form a scaffolding for the cellular proliferation and new tissue formation, and so modify the ultimate histological architecture of the tumour.

Whilst the histological study of this case, therefore, suggests the importance of the schwann cells, the nature of the associated lesions also favours this suggestion. It is now more or less accepted that the neurilemmal cells develop from the neuroectodermic crest, and hence have ultimately the same origin as the ganglion cells and the cells of the adrenal medulla. Hence the association of the chromaffinoma and the ganglioneuroma in this case would support the idea that von Recklinghausen's disease has its origin in some congenital abnormality of the neuroectodermic crest. The association between neurofibromatosis and tumours of the adrenal medulla has also been noted by Zuzuki (1909), Kawashima (1911), and others. Such an idea is further supported by the occasional occurrence of lesions in the central nervous system—gliomas of the optic chiasm (Bailey) bilateral acoustic neurinomas. In a few cases the central lesion has been tuberous sclerosis (Orzewski and Howicki, Bassoe and Nuzum), and even in patients free from the stigmata of this process, small glial nodes may be found scattered throughout the brain and spinal cord. It might be suggested, therefore, that some congenital abnormality of the neuroectoderm may result in a closely-related variety of lesions—tuberous sclerosis, central, or peripheral von Recklinghausen's disease. These lesions may occasionally occur together, or only one manifestation of the defective anlage may be present.

The other points of interest arising in the present case are : (1) the widespread involvement of the autonomic nervous system, (2) the chromaffinoma, and (3) the malignant transformation of the cervical nodule. The case as a whole duplicates in these points that described by Herxheimer and Roth (1914). Their case showed multiple tumours of the skin, tumours of the intercostal and lumbar nerves, a large pelvic sarcoma, a chromaffinoma of the adrenal medulla, and multiple subserous

nodules on the jejunum. Widespread involvement of the autonomic nervous system has been noted by Czerny, Harbitz, and Verocay.

Chromaffinoma of the adrenal is frequently associated with paroxysmal hypertension, but the clinical record in this case gives no indication of this having occurred, though the period of observation is too short to be conclusive. The curious growth of this tumour into the adrenal vein without metastases has also been noted by Manasse (1893).

Malignant transformation of a nodule is not infrequent. This may be manifested by an increase in cellularity of the tumour without any marked changes in its histological pattern. Such active areas are found in the present case in some of the splanchnic nerves, in the left brachial plexus, etc., and in the event of biopsy, one would have hesitated to pronounce them benign. In his recent review of these tumours, Stout (1935) states that they rarely metastasize, though they tend to recur locally. The extensive involvement of the nerve trunks, however, by the proliferative process renders the idea attractive that the subsequent growth near the site of removal may be, not a recurrence in the usual sense of the term, but a recrudesence of cellular activity in the same or in an adjacent nerve. From the nature of the process it is obviously impossible to remove all the affected tissue, for as is seen in this case, the cellular proliferation may extend as far as the muscle spindle, or the terminal nerve-twigs around the sweat-glands or the blood-vessels. The possibility of multiple sites of cellular activity may also be held to influence treatment. Habermann, for example, reported a case in which primary malignant growths were found in the sciatic, ulnar, and occipital nerves.

The malignant tumour in the right supraclavicular region, however, is not merely a rapidly-growing nodule. Here the histological picture is that of a spindle-cell sarcoma, and it is surprising, in view of the extensive invasion of the blood-vessels, that no metastases were found. However, in a series collected by Stout of ninety-one cases of malignant change in von Recklinghausen's disease, only eighteen (twenty per cent.) showed metastases. In the present case it was impossible to demonstrate any axis cylinders or myelin sheaths in the sarcoma—this finding agreeing with the clinical history of the recent development of paralysis in the arm-muscles. It would seem, therefore, that the occurrence of motor-paresis in a patient with neurofibromatosis is at least suggestive of malignant change, for even large benign nodules on the course of a nerve interfere little, if at all, with motor function, though there may be some sensory loss.

Finally, it may be noted that the nodules may be stimulated to active growth by conditions which are associated with changes in the endocrine organs. Thus in pregnancy, latent nodules may become apparent, and others rapidly increase in size. With the cessation of the puerperium, growth diminishes, but may reappear in a subsequent pregnancy. Of interest in this connection is the recent observation by Ferguson (1935), that the blood of patients suffering from von Recklinghausen's disease, neurosarcoma, and malignant melanoma contains the hormone intermedin —the melanophoric hormone of the hypophysis.

SUMMARY.

(1) A case of generalised von Recklinghausen's disease is reported.

(2) The generalised subcutaneous tumours were associated with tumours on the deep nerves, marked changes on the autonomic nervous system, neurosarcoma in the right brachial plexus, chromaffinoma and ganglio-neuroma of the adrenal.

BIBLIOGRAPHY.

1. BASSOE, P. AND NUZUM, F. (1915): *Jour. Nerv. and Mental Disease,* xlii, 785.
2. COPELAND (1935): *Amer. Jour. Cancer,* xxiv, 751.
3. CZERNY: Quoted by Ewing, "Neoplastic Diseases."
4. FERGUSON: Quoted by Copeland.
5. HERXHEIMER AND ROTH (1914): *Zeigler Beit.,* lviii, 319.
6. HARBITZ, F. (1909): *Arch. Int. Med.,* iii, 32.
7. KAUFMANN: *Pathology,* vol. iii (translated by Reiman), London (1929).
8. KAWASHIMA (1911): *Virch. Arch.,* cciii, 66.
9. MANASSE (1893): *Virch. Arch.,* cxxxiii, 391.
10. MASSON (a) (1932): *Amer. Jour. Path.,* viii, 367 and 389; (b) (1935): *Bull. Soc. franc. de Dermat.,* xlii, 1278.
11. ORZECHOWSKI AND NOWICKI (1912): *Seit. f. d. ges. Neur. u. Psych.,* xi, 237.
12. STOUT (1935): *Amer. Jour. Cancer,* xxv, 1.
13. VEROCAY (1910): *Zeigler Beit.,* xlviii, 1.
14. ZUZUKI (1909): *Berlin. Klin. Wochenschr.,* xxxvi, 1644.

Simmonds' Disease

By J. H. BIGGART,

Institute of Pathology, Queen's University, Belfast

THE description by Paulesco in 1907 of the symptoms developing in dogs after extirpation of the anterior pituitary was followed in 1914 by Simmonds' now classic paper demonstrating the clinical picture in man which he correlated with destruction of the anterior pituitary by disease. In recent years such cases have attracted much attention, and over two hundred have been reported in the literature, of which few more than one-third have been verified by post-mortem study. In an extensive review in 1933, Silver found forty-one cases so confirmed, in 1936 Howard and Rhea mention a total of forty-seven proven cases, whilst in 1938 Lisser and Ascarilla collected sixty-nine. Sheehan (1939) calculates that in each ten thousand of the population there are about two severe and seven lesser examples of hypopituitarism, but post-morten findings have so far failed to reveal this high incidence. Unfortunately, in many recent papers some confusion has arisen between the clinical picture of Simmonds' Disease and anorexia nervosa, and it has become more than ever necessary to insist upon the post-mortem verification of the diagnosis whilst we await the development of some clinical observation or biological test which will more clearly separate these two conditions.

In view of the still relative rarity of confirmed cases, and in order that any

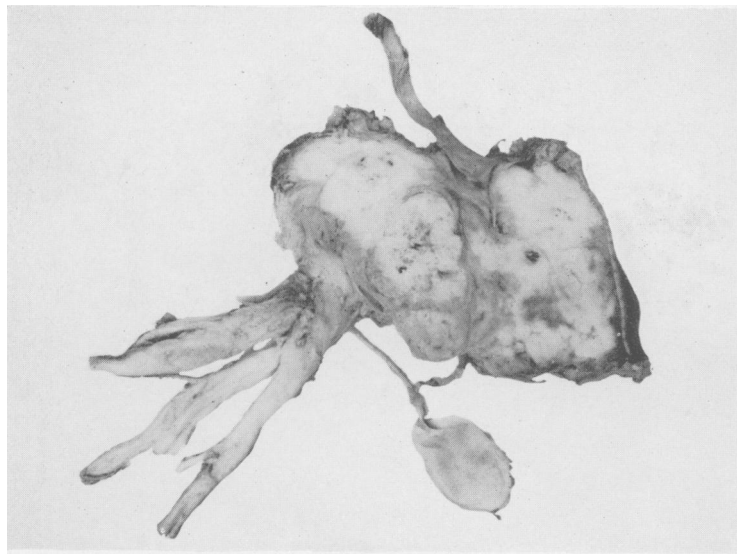

Fig. 1

Tumour of right supraclavicular region, showing involvement of brachial plexus. Note the thickening of the brachial plexus, and the swelling on the nerve to the Teres major. One-third natural size.

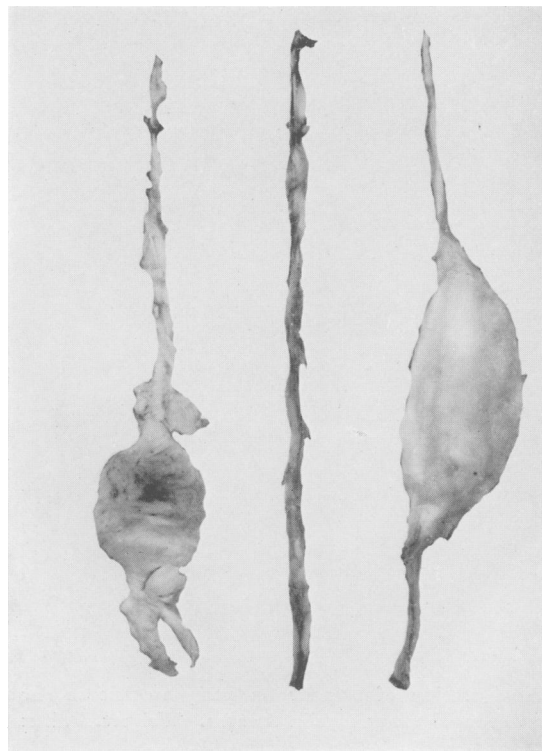

Fig. 2

To show the varied appearances found on the peripheral nerves. The illustration shows the right thoracic sympathetic chain, the ileo-inguinal nerve, and the left external peroneal nerve.

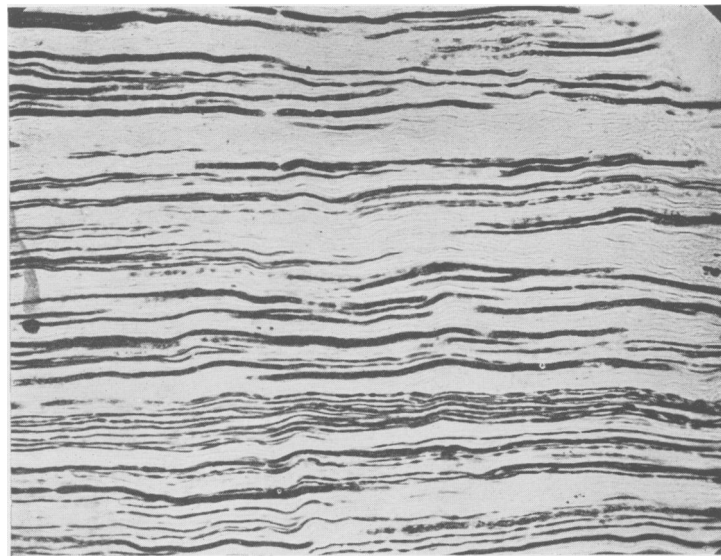

Fig. 3
Longtitudinal section of a nerve showing diffuse thickening. The myelin sheaths are separated by fibrous tissue lying parallel to the nerve fibres. Weigert. Pal. x 110.

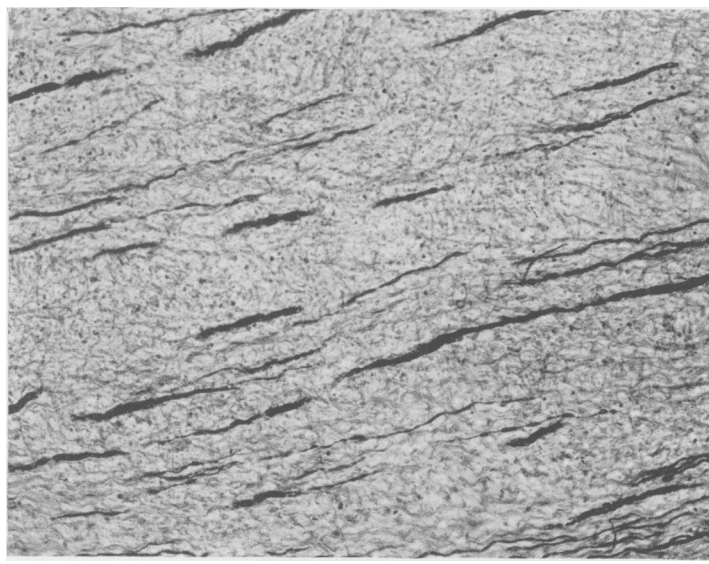

Fig. 4
Longtitudinal section of tumour on peripheral nerve showing the preservation of many myelin sheaths. Weigert. Pal. x 110.

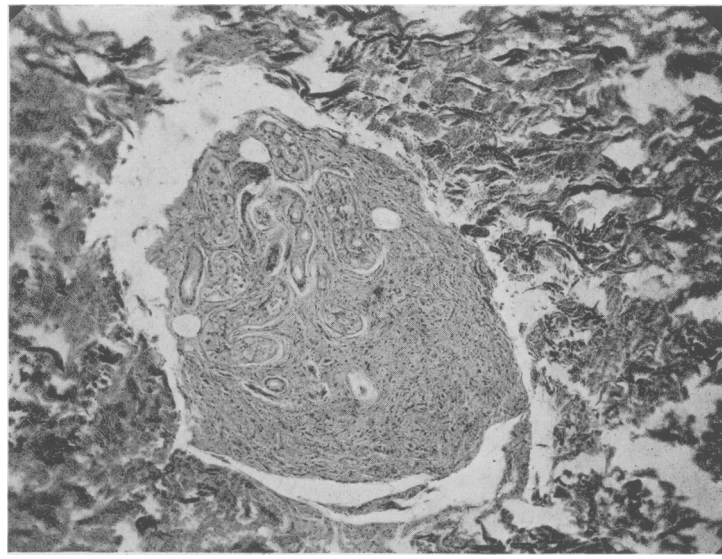

Fig. 5

Small neurofibromatous nodule surrounding sweat-glands. x 75.

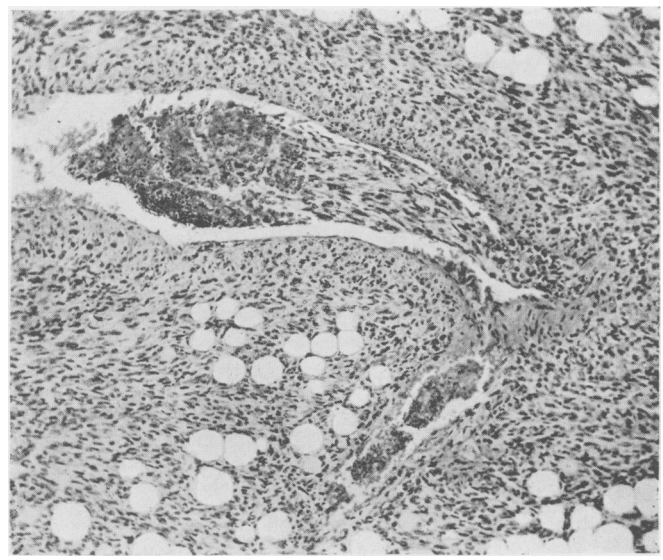

Fig. 6

Neurosarcoma. Section from right supra-clavicular tumour, showing invasion of a blood-vessel and adjacent fat. The tumour is composed of non-specific spindle cells.

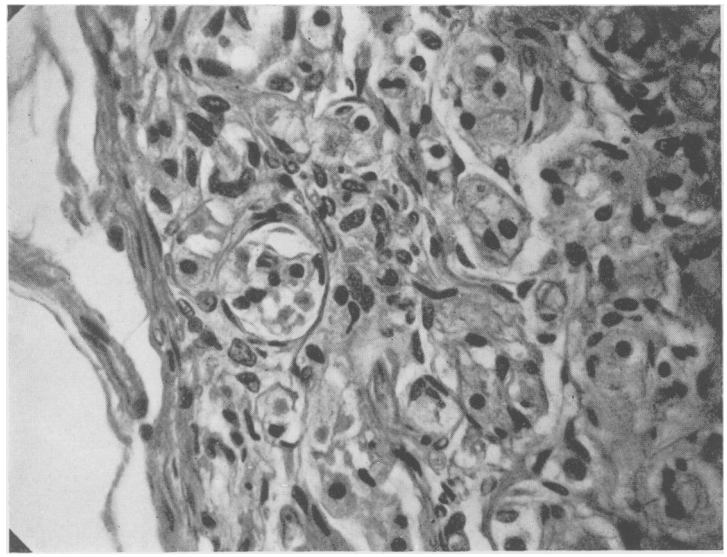

Fig. 7

Section from a cellular area from a nerve in the pancreas. Note the cellular proliferations in relation to individual nerve-fibres. x 600.

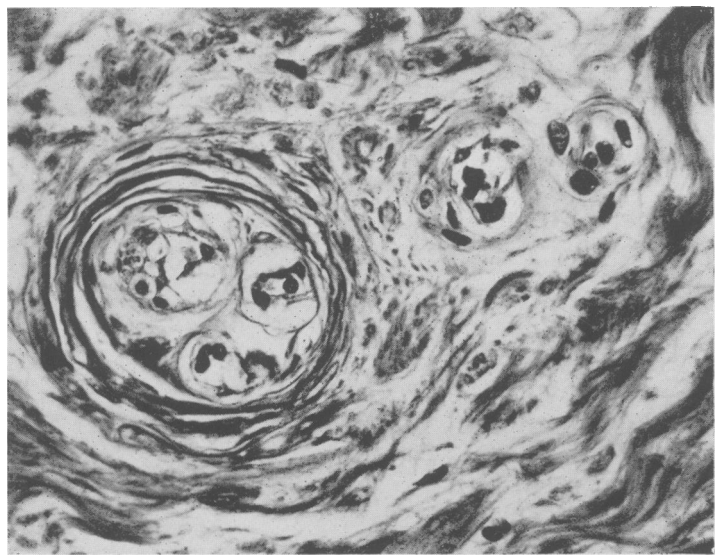

Fig. 8

Section from a tumour nodule, showing cellular proliferations in relation to surviving nerve-fibres. x 600.